Diazapolycyclic Compounds. XX. Stereochemistry of some Addition Reactions to the Double Bond at the Terminal Tetrahydropyridazine Ring of Methyl Substituted 4a,12a-Diaza-1,4,4a,5,12,12a- and 4a,12a-Diaza-3,4,4a,5,12,12a-hexahydronaphthacene-5,12-diones, and the Corresponding Epoxides (1)

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The stereochemistry of *N*-bromosuccinimide electrophilic additions to the double bond at the terminal tetrahydropyridazine ring moiety of the 4a,12a-diazatetracyclic compounds **1-4** has been studied. These reactions appear as very regio- and stereoselective. Most the of the results obtained support the hypothesis that the *N*-bromoamide additions to cyclohexenes and heterocyclic analogous do not occur *via* the usual Ad_{E_2} mechanism, because the nucleophilic step is the rate-limiting one and the main product-determining factor. On the other hand, epoxidation of the double bond in **1-4** and further opening of the oxirane ring take place in accordance with the normal stereochemical rules.

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In the course of our investigations on the synthesis, structure and reactivity of some 4a,12a-diazatetracyclic systems, methyl substituted 4a,12a-diaza-1,4,4a,5,12,12a-hexahydronaphthacene-5,12-diones like **1** or **2** have been described (2-4). Isomerization in acid medium of the double bond at the terminal tetrahydropyridazine ring moiety (ring A) led to structures like **3** or **4** (5). A wide variety of derivatives have been prepared from all these compounds by different types of reactions performed on ring A, several of them including electrophilic additions of *N*-bromosuccinimide (NBS) to the double bond. These NBS additions show unexpected regio- and stereoselectivities, contrary to what should be observed if the reaction followed the classic Ad_{E_2} pathway. As a matter of fact, increasing evidence has been accumulating in recent times for a different mechanism in additions of *N*-haloamides to substituted cyclohexenes (6-8) and dihydropyrans (9). In it, the rate-determining step should not be an irreversible electrophilic one, as it happens in the Ad_{E_2} reactions. Therefore, the stereoselectivity of the reaction should not be controlled by this electrophilic step. Berti and his co-workers have proposed that, in some electrophilic additions, the electrophilic step is reversible, and both the regio- and stereoselectivity are determined by steric or electronic effects operating during the nucleophilic step, which should be the rate-limiting one. The available data support this interpretation mainly in *N*-bromoamide additions, but also for other electrophiles such as hypoiodous acid, iodine azide (10) and mercuric acetate (11).

In connection with this matter, we report here the stereochemical behavior of the tetrahydropyridazine ring moiety of our diazatetracyclic compounds towards NBS additions. Results obtained in the nucleophilic opening of the corresponding epoxides are also included, since it has been pointed out that they can be taken as models for the nucleophilic step of these electrophilic additions (8). Reactions performed, structures synthesized and stereochemical results obtained are summarized in Scheme 1.

Treatment of compounds **1-4** with *N*-bromosuccinimide in an aqueous suspension containing some drops of sulphuric acid afforded the bromohydrins **5-8**. When the same reaction was performed on **3** and **4** in absolute ethanol solution, the ethoxyl group acted as the nucleophile (12) to give **9** and **10**. Compounds **5**, **7** and **9** were obtained as the only isomers in good yields, but slightly contaminated with minimal amounts of the corresponding dibromides, which were separated by preparative thin layer chromatography or simple recrystallisation. This applies also for the formation of **6**, although a small amount of the 2-bromo-3-hydroxy isomer (8% of the whole yield) was isolated here. The NBS addition product **11** was also formed in a high yield in the same reaction as the bromohydroxy derivative **9**. This is not a surprising result, because it has been previously obtained as the only product when performing NBS reactions under free radical conditions on analogous diazatetracycles (5). During the preparation of **8** and **10** cleavage of the N-C_1 bond also occurs, to give a mixture of ring A opening compounds, although **8** and **10** are by far the major reaction products. In fact, the reaction temperature must be lower in the synthesis of these compounds than in the case of **7** and **9**, in order to avoid ring-opening to a great extent.

The stereochemistry of ring A in these new derivatives was determined on the basis of ^1H nmr spectroscopic data, taking advantage of the large experience accumulated in previous work on the spectroscopic features of the piperidazinic protons in resembling 4a,12a-diazatetracyclic systems. It was difficult to establish the position of the bromine and the hydroxy group in bromohydrin **5**, since the signals corresponding to protons H_2 and H_3 could not be easily differentiated. Thus, it was necessary to prepare

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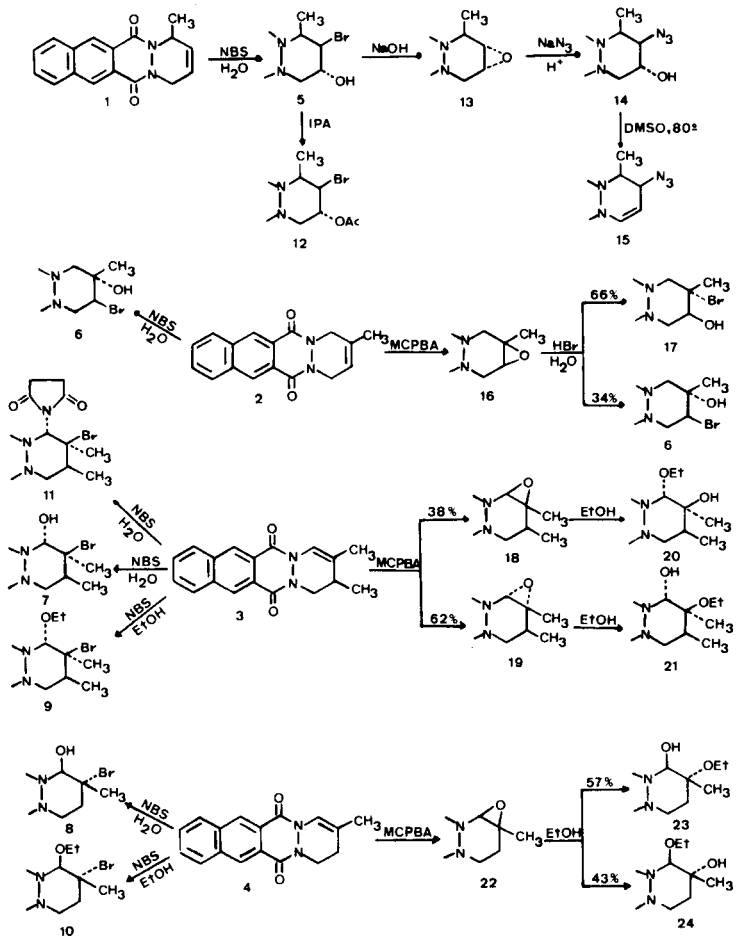
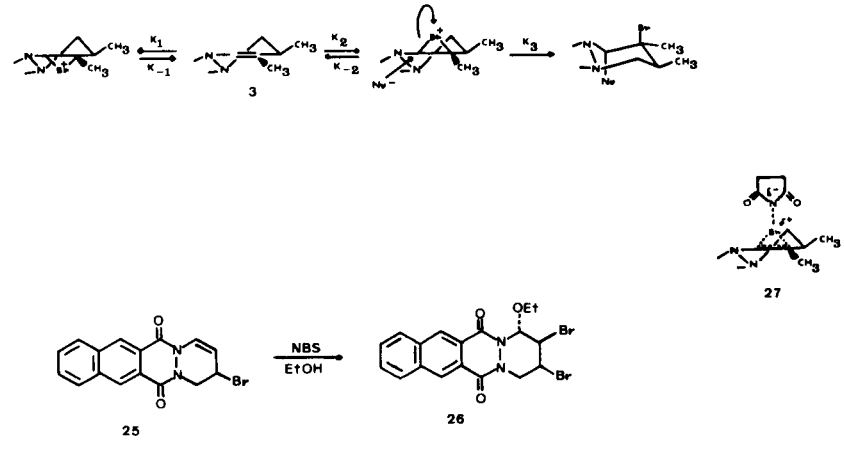


Scheme 1



Scheme 2

the acetyl derivative **12**, in which the signal corresponding to the ring proton geminal to the acetoxy group moves downfield about 1.1 ppm, as can be seen in Table 1. This fact allows the identification of every proton in the spectrum by means of double resonance techniques. The small value found for the coupling constants between H_3 and the methylenic H_4 and $H_{4'}$ in both **5** and **12** ($\leq$ 3.3 Hz) indicates an equatorial orientation for H_3 and, consequently,

Table 1

Some ^1H Nmr Data of the New 4a,12a-Diazatetracyclic Compounds (a)

Compound No.	δ H_1	δ H_3	δ H_4	δ H_4'	δ H_6, H_{11}	δ Me-C_2	$J_{3,4}$	$J_{3,4'}$	$J_{4',4'}$	Other Significant Data
5	5.35 (o)	4.26 (m)	4.94 (m)	4.04 (dd)	8.78 (s)	—	3.3	2.8	14.0	δ H_2: 4.58 (m); $J_{1,2}$: 3.2; $J_{2,3}$: 5.8; δ Me-C_1: 1.48 (d)
6	δ H_1, δ H_3, δ H_4: 4.40-4.60, W ½: 3.0				8.92 (s)	1.50 (s)	—	—	—	δ OH: 5.85 (s); δ H_1', δ H_4': 4.05-4.25, W ½: 3.0
7	6.35 (d)	2.25 (m)	4.80 (dd)	3.15 (dd)	8.90 (s) 8.95 (s)	1.90 (s)	4.5	12.0	13.5	δ Me-C_3: 1.10 (d)
8	6.40 (bs)	2.30 (m)	5.02 (m)	3.4-4.0 (b)	8.98 (m)	2.00 (s)	—	—	—	
9 (c)	6.40 (bs)	2.35 (m)	4.90 (dd)	3.35 (t)	9.00 (s)	2.00 (s)	5.5	12.0	12.0	δ Me-C_3: 1.15 (d)
10	6.35 (s)	2.35 (m)	5.05 (o)	3.3-4.1 (b)	9.05 (s)	2.05 (s)	3.5	5.0	13.0	
11	7.35 (s)	2.70 (m)	5.05 (c)	3.60 (c)	8.78 (s)	1.90 (s)	6.0	12.0	13.3	δ Me-C_3: 1.20 (d)
12	5.48 (o)	5.33 (m)	5.04 (m)	4.10 (dd)	8.72 (s)	—	2.4	2.6	14.5	δ H_2: 4.42 (m); $J_{1,2}$: 3.0; $J_{2,3}$: 5.6; δ Me-C_1: 1.45 (d)
15 (d)	δ H_1, δ H_3: 5.4-6.0		7.98 (bs)	—	9.00 (s)	—	W½:3.0	—	—	δ Me-C_1: 1.35 (d); H_2: 3.95 (m), W ½: 10.0
17	5H piperidazine ring moiety:3.8-4.8				8.75 (s)	1.90 (s)	—	—	—	δ OH: 6.20 (d)
20	5.85 (s)	2.45 (m)	4.68 (o)	3.18 (m)	8.95 (s)	1.05 (s)	7.0	12.0	16.0	δ Me-C_3: 1.0 (d)
21	6.05 (d)	2.55 (m)	5.0 (dd)	3.10 (m)	8.75 (m)	1.38 (s)	4.5	13.5	12.0	δ Me-C_3: 1.12 (d)
23	6.10 (bs)	2.0-2.6 (b)	4.83 (m)	3.2-3.8 (e)	8.70 (s)	1.55 (s)	—	—	—	
24	6.05 (s)	2.0-2.6 (b)	4.75 (m)	3.2-3.8 (e)	8.95 (s)	1.48 (s)	—	—	—	

(a) Spectra measured in perdeuteriodimethyl sulphoxide (internal TMS) solution, unless otherwise stated. Most of the assignments have been confirmed by double resonance experiments. Shifts are given in ppm. Coupling constants are given in Hz. Only the more relevant data are given in this Table. The nmr spectra of these compounds will be discussed elsewhere in detail. Abbreviations: b = broad, d = doublet, t = triplet, dd = double doublet, o = octet, m = multiplet. Numbering of the hydrogens is referred to that employed for the attached carbon atoms in the experimental part. (b) This signal is overlapping with that of H_3. (c) Recorded in deuteriochloroform. (d) Recorded in deuteriochloroform. In spite of the double bond formed at the terminal piperidazine ring moiety, the numbering used in the other compounds has been maintained here, in order to facilitate comparisons. (e) This signal is overlapping with that of the methylene at the ethoxy group.

for H_2, owing to the generality of the rule of *anti* additions to alkenes. On the other hand the great difference found between $J_{1,2}$ and the smaller $J_{2,3}$ can be explained on the basis of the axial orientation assigned to H_1, not only due to the fact that J_{aa} values are greater than the J_{ae} ones in heterocyclic derivatives (and also in these compounds), but also because the reducing influence of an electronegative substituent (bromine) upon J_{vic} is greatest when it is transcoplanar to one of the coupling protons (H_1) (13). The characterization of bromohydrin **6** was described in a previous paper (14). In compounds **7** and **9**, the chemical shift values found for the methyl group at C_2 (a singlet centred at 1.9 and 2.0 ppm, respectively) are evidence for an equatorial position, geminal to the bromine atom, as can be seen by comparing with the *trans*-dibromide nmr data (5). When hydroxy or ethoxy groups are attached to C_2, the methyl signal appears at fields consistently higher. Moreover, the presence of hydrogen bonding between the hydroxy group and the nearby carbonyl can be detected in the ir spectrum of **7** (broad hydroxy band from 2600 to 3400 cm^{-1}, shift of the C=O bond from its usual position) (15). It is the cause of the different nmr chemical shifts observed for the two aromatic protons at ring C, which usually appear as a unique singlet in these compounds. The mentioned hydrogen bonding is probably responsible for the difficulties found in the acetylation of **7** when the same mild conditions used in the preparation of **12** were employed. In the ABX system formed by the methylenic protons H_4 and H_4' and the methinic H_3, the coupling constant between the methylenic axial H_4' and H_3 is 12 Hz in both **7** and **9**. This result is evidence for an axial orientation of H_3 and an equatorial one for the geminal methyl group. The appearance of the H_1 signals at fields as low as 6.35 and 6.40 ppm is in accordance with the equatorial arrangement of this proton, falling under the deshielding influence of the carbonyl group. Spectroscopic data obtained for compounds **8** and **10** are similar to those mentioned above for **7** and **9**. They also show the methyl group to be attached to the same carbon that the bromine atom, and both new substituents to be in a *trans*-diaxial disposition.

Treatment of the bromohydrin **5** with aqueous sodium hydroxide led to the epoxide **13**, which was opened with sodium azide in acetic acid to give the hydroxyazide **14** as the major reaction product. The presence of a minor product was detected by analytical thin layer chromatography, but it could not be isolated in enough yield for identification. The position of the azido and hydroxy

groups in **14** could not be assigned on the basis of the available spectroscopic data, but further dehydration by heating at 80° in dimethyl sulphoxide solution afforded **15**. In this last compound, the vicinal disposition of the azido and methyl groups was established from its nmr spectrum. This assignment is mainly supported by the appearance of the signal corresponding to one of the ring A protons at a field as low as 7.9 ppm, since it only may be due to an ethilenic hydrogen under the influence of the deshielding effect of the nearly carbonyl group (16).

When the epoxide **16** (obtained by *m*-chloroperbenzoic acid oxidation of **2**) was treated with 50% aqueous hydrobromic acid in methanol at 50°, the two isomeric bromohydrins **6** and **17** were formed in a 60/40 ratio. Both isomers are easily differentiated by their nmr spectra, as it has been previously reported by us (14).

Oxidation of adduct **3** with *m*-chlorobenzoic acid in chloroform solution afforded a mixture of the isomeric epoxides **18** and **19** which were not isolated, but directly opened to the hydroxyethers **20** and **21** while performing a preparative thin layer chromatography with a benzene/ethanol mixture as eluent. Both isomers were obtained in a 38/62 ratio. The main differences in their nmr spectra are the relative shielding of the C_2 methyl group in **21** relative to **20** (0.2 ppm) and the non-equivalence shown by the aromatic protons at the ring C moiety in **21**, probably due to interaction between the hydroxy group and the nearby carbonyl, as exposed above for bromohydrin **7**. The ir spectrum of **20** shows the C-O absorption at 1110 cm^{-1}, while that of **21** has the C-O signal at 1030 cm^{-1}, in accordance with the expected differences between tertiary and secondary hydroxy groups (17).

In a similar way, compound **4** was directly converted to the mixture of isomers **23** and **24** by oxidation with *m*-chloroperbenzoic acid in chloroform-ethanol solution. The distribution of both stereoisomers proved to be 57% (**23**) and 43% (**24**) as established by integration of the nmr spectrum. The differences found between the spectroscopic data of these two compounds are analogous to those mentioned above for **20** and **21**.

By comparing the results depicted in Scheme 1, it is clear that the NBS addition reactions to the double bond exhibit a higher regioselectivity than the oxirane ring-opening ones do. The orientation of this regioselectivity is different in both types of reactions. The usual rules are always followed in the opening of epoxides, since the major product is formed by nucleophilic attack at the less substituted carbon. On the contrary, the NBS additions proceed in the anti-Markownikoff sense, except in the case of **6**. These facts might be interpreted on the basis of an anomalous reaction pathway in the presence of NBS, according to the hypothesis proposed in previous work.

In the NBS reactions performed on **1** and **3**, the formation of the *trans*diaxial compounds **5**, **7** and **9** is indicative of a high *syn*-stereoselectivity in the attack by electrophilic bromine with respect to the methyl substituent, leading to the *cis*-epibromonium ion, less stable than the *trans* one. This is not consistent with the classic Ad_{E_2} pathway, in which the more stable bromonium ion should be formed by irreversible electrophilic attack, determining the nature of the reaction products. In the light of earlier work (6-11), it seems more likely the alternative mechanism involving the formation of the more reactive *cis* intermediate and the reversibility of the electrophilic step, which is followed by a slow rate of nucleophilic attack. Hence, the steric and stereoelectronic effects operating during the nucleophilic step should be the main product-determining factor. Scheme 2 exemplifies the regio- and stereoselectivity of NBS addition to **3**, implying that $K_3 < K_1, K_2$ and $K_2 < K_{-1}$. The high preference for *syn* attack would be therefore due to the fact that the *cis*-epibrominium ion **3a** more readily undergoes nucleophilic opening for stereoelectronic reasons. It has been suggested that the epibromoniun ions should be bonded to the succinimido group, as shown in **27**, by assuming that this kind of intermediate would be formed more readily and, being less reactive than the epibromonium ion itself, could undergo a slow-rate nucleophilic attack (8,18).

On the other hand, the steric effects apparently predominate over the electronic ones in these reactions. The formation of **5** occur in the anti-Markownikoff sense, in spite of the stabilizing effect of the C_1 methyl group. The same pattern is followed in **7** and **9**, involving, in addition, nucleophilic attack at the ring carbon that is nearest to the nitrogen atom and more subjected to its unfavorable inductive effect. However, it is not so in the case of **6**, because of the absence of the steric requirements for the formation of a *cis*-bromonium ion introduced by the respective methyl groups in compounds derived from **1** or **3**. The results obtained in the NBS reactions of **4** are quite surprising, because it should be expected for **8** and **10** the same regioselectivity found in **6**. It seems difficult to find a satisfactory explanation for this behavior on the basis of the exposed steric and electronic arguments. A steric hindrance of the methyl group at C_2, obstructing the attack of the nucleophile on this position, appears as a very unlikely hypothesis. The different position of the double bond in **4** with respect to **2** could perhaps favor some kind of interaction between the nucleophile and the neighbouring amido group, and further attack at the nearest carbon atom during the rate-limiting nucleophilic step, but we defer commenting on this hypothesis until more evidence can be obtained.

With regard to the epoxidations and further ring-opening reactions, it must be noted that results obtained agree with the mechanism usually followed by them. Thus, the formation of the hydroxyazide **14** from **13** is directed by the inductive effect of the neighbouring methyl group,

which prevails over the steric hindrance with the incoming nucleophile (the antiparallel attack is, of course, another reason). The same pattern applies in the opening of epoxides **16** and **22**, where the nucleophilic attack takes place at the more substituted carbon atom. In the *m*-chloroperoxybenzoic acid reaction of the isomerized compound **3**, the more stable *trans*-isomer **20** is the major product, in accordance with the usual stereoselectivity rules (19).

The opening of both types of cyclic intermediates, epoxides and epibromonium ions, always takes place in a *trans*-diaxial manner, and the stereoelectronic requirements in the nucleophilic attack are prevailing over the inductive effect. Thus, as shown in scheme 2 for compound **3**, the nucleophilic attack at C_2 to give the *trans*-diaxial derivative should occur in a parallel direction with respect to the axial proton at C_1, through a boatlike transition state. However, reaction at C_3 proceeds *via* a chairlike transition state and therefore must be highly favored (20). The same argument applies, for example, in the opening of epoxide **13**: parallel attack of the azido ion at C_3 is not favored, and the *trans*-diaxial derivative is formed owing to the more suitable conformational requirements.

Finally, we would like to revisit here the results reported by us in a previous paper referring to the NBS treatment of compound **25**, which afforded the isomer **26** in a stereospecific way (14). The stereochemical implications of this reaction were not discussed there. Now, this stereochemistry can be easily explained on the basis of the arguments exposed above. The reaction proceeds *via* an electrophilic *syn*-addition of the positive bromine with respect to the substituent at C_3. After that, the nucleophilic attack takes place at the C_1 position, because of the unfavorable stereoelectronic effects that should appear in the parallel attack at C_2. Therefore, the formation of **26** strictly parallels the conversion of **3** into **7** or **8**, providing further justification for the previous reasonings.

In consequence, it seems that the mechanism proposed for the NBS additions to cyclohexene derivatives could also be operative in these diazatetracyclic compounds. Some work concerning the stereoselectivity in the addition reactions of halogen azides is now in progress, and will be shortly published.

EXPERIMENTAL

Melting points are uncorrected, and were determined in open capillary tubes with a Gallenkamp apparatus. Ir spectra were recorded on a Perkin-Elmer 250 spectrophotometer. Nmr spectra were obtained with Perkin-Elmer R-12 and Varian XL-100 spectrophotometers. Direct inlet mass spectra were determined in a Varian MAT spectrophotometer. Thin layer chromatography plates were prepared with silica gel G (Merck).

Compounds **1-4** were obtained by cycloaddition reactions between benzo[*g*]phthalazine-1,4-dione and the corresponding dienes, according to procedures previously described by us (2,3,5). The syntheses of epoxides **13** and **16**, and the preparation of bromohydrin **6** by NBS addition to **2** have also been reported in former papers (2,14).

1-Methyl-2-bromo-3-hydroxy-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**5**).

To an aqueous suspension of finely divided **1** (0.5 g. or 1.8 mmoles in 30 ml.), 0.38 g. (2.1 mmoles) of freshly recrystallised *N*-bromosuccinimide and 3 drops of concentrated sulphuric acid were added. The mixture was vigorously stirred for 24 hours at 50°. During this time, the starting orange suspension was slowly decolorised. After cooling at room temperature, the reaction mixture was filtered to give a pale yellow solid which was repeatedly washed with water. Thin layer preparative chromatography of this solid in benzene/ethanol (9/1) as eluent led to the isolation of two compounds. The less retained one was identified as the dibromide, and only 0.1 g. were obtained. The more retained solid recrystallised from water affording 0.43 g. (64% yield) of **5**, m.p. 148-150°; ir (nujol): ν max 3000-3500 (OH), 1655 (C=O), 1615, 1460, 1380, 1360, 1255, 1210, 1060 (secondary OH), 760 cm^{-1}.

Anal. Calcd. for $C_{17}H_{15}BrN_2O_3$: C, 54.40; H, 4.00; Br, 21.33; N, 7.47. Found: C, 54.40; H, 4.16; Br, 21.03; N, 7.78.

1-Hydroxy-2-bromo-2,3-dimethyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**7**).

This compound was prepared as described above for **5** from 1 g. (3.4 mmoles) of **3** and 0.65 (3.6 mmoles) of NBS in 50 ml. of water, to give a white solid which recrystallised from acetone affording 1.17 g. (97% yield) of **7**, m.p. 152-154°; ir (nujol): ν max 2600-3500 (OH), 1670 (C=O), 1650 (C=O), 1625, 1465, 1320, 1200, 1040 (secondary OH), 770 cm^{-1}; ms: m/e (% relative abundance) 389 (4, M^+), 360 (1), 290 (85), 289 (33), 275 (9), 261 (9), 242 (14), 234 (14), 233 (19), 210 (14), 155 (33), 154 (42), 126 (90), 99 (100).

Anal. Calcd. for $C_{18}H_{17}BrN_2O_3$: C, 55.52; H, 4.37; Br, 20.56; N, 7.20. Found: C, 55.86; H, 4.54; Br, 20.35; N, 7.30.

1-Hydroxy-2-bromo-2-methyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**8**).

To an aqueous suspension of finely divided **4** (1 g. or 3.6 mmoles in 50 ml.), 0.65 g. (3.6 mmoles) of freshly recrystallised *N*-bromosuccinimide and one drop of concentrated sulphuric acid were added. The mixture was vigorously stirred for 24 hours at room temperature. Then, the pale yellow reaction mixture was filtered to give a creamy solid which was washed repeatedly with water. Thin layer preparative chromatography in benzene/ethanol (94/6) afforded a white solid. Recrystallisation from water/acetone gave 0.46 g. (36% yield) of pure **8**, m.p. 134-136°; ir (potassium bromide): ν max 3000-3600 (OH), 1660 (C=O), 1640 (C=O), 1615, 1390, 1370, 1280, 1260, 1030 (secondary OH), 805, 755 cm^{-1}.

Anal. Calcd. for $C_{17}H_{15}BrN_2O_3$: C, 54.40; H, 4.00; Br, 21.33; N, 7.47. Found: C, 54.53; H, 4.02; Br, 21.02; N, 7.70.

1-Ethoxy-2-bromo-2,3-dimethyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**9**).

To a stirred suspension of 1 g. (3.4 mmoles) of **3** and 0.6 g. (3.4 mmoles) of freshly recrystallised *N*-bromosuccinimide in 50 ml. of "dry" benzene, 5 ml. of absolute ethanol were added, and the mixture was heated at 50° for five hours. After stirring for one additional hour at room temperature, the suspension was filtered to give a yellow solid. Thin layer preparative chromatography in benene/ethanol (9/1) as eluent afforded three compounds. The more retained one, from which 0.35 g. were obtained, was identified as 1-succinimido-2-bromo-2,3-dimethyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**11**). The intermediate compound was shown to be the corresponding 1,2-dibromoderivative (0.10 g.). The less retained product was identified as **9**, and 0.28 g. (20% yield) were obtained, m.p. 141-142°; ir (nujol): ν max 1655 (C=O), 1625, 1460, 1390, 1380, 1320, 1260, 1215, 1195, 770 cm^{-1}; ms: m/e (% relative abundance) 417 (5, M^+), 375 (4), 337 (42), 291 (18), 280 (34), 279 (100), 238 (22), 210 (24), 180 (30), 154 (14), 127 (15), 126 (34).

Anal. Calcd. for $C_{20}H_{21}BrN_2O_3$: C, 57.55; H, 5.03; Br, 19.18; N, 6.71. Found: C, 57.44; H, 4.87; Br, 19.46; N, 6.76.

1-Ethoxy-2-bromo-2-methyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**10**).

To a stirred suspension of 0.5 g. (1.8 mmoles) of **4** in 30 ml. of absolute ethanol, 0.33 g. (1.8 mmoles) of freshly recrystallised *N*-bromosuccinimide and two drops of concentrated sulphuric acid were added, and the mixture was heated at 50° for three hours. Then, stirring was maintained at room temperature for 12 hours more. After that, 15 ml. of ethanol were removed by evaporation under reduced pressure, and 30 ml. of water were added to the residue. Filtration of the resulting suspension afforded a yellow precipitate, which was chromatographed by using ether/petroleum ether/chloroform (5/5/1) as eluent to give 0.3 g. (42% yield) of the title compound and a minor amount of the corresponding 1,2-dibromoderivative, m.p. 183-184°; ir (potassium bromide ν max 3065, 2990, 2940, 1650 (C=O), 1625, 1450, 1400, 1310, 1280, 1215, 1180, 760, 725 cm^{-1}; ms: m/e (% relative abundance) 404 (8), 402 (8, M^+), 359 (3), 323 (18), 294 (1), 278 (8), 265 (100), 225 (8), 197 (8), 180 (13), 154 (8), 127 (26), 112 (7).

Anal. Calcd. for $C_{19}H_{19}BrN_2O_3$: C, 56.57; H, 4.71; Br, 19.85; N, 6.95. Found: C, 56.33; H, 4.77; Br, 20.10; N, 6.92.

1-Methyl-2-bromo-3-acetoxy-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**12**).

To a suspension of the bromohydrin **5** (0.5 g. or 1.3 mmoles) in 50 ml. of isopropenyl acetate a catalytical amount of *p*-toluenesulphonic acid was added, and the mixture heated under reflux for 2 hours. The resulting dark-brown solution was successively washed with 50 ml. of 10% aqueous sodium bicarbonate and 50 ml. of water. The organic layer was then dried over magnesium sulphate and evaporated *in vacuo* to give a solid which recrystallised from ethanol affording 0.38 g. (69% yield) of **12**, m.p. 207-210°; ir (nujol): ν max 1740 (C=O acetate), 1655 (C=O) 1625, 1455, 1375, 1355, 1315, 1230, 1210, 755 cm^{-1}.

Anal. Calcd. for $C_{19}H_{17}BrN_2O_4$: C, 54.67; H, 4.07; Br, 19.18; N, 6.71. Found: C, 54.51; H, 4.14; Br, 19.29; N, 6.71.

1-Methyl-2-azido-3-hydroxy-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**14**).

A solution of 0.5 g. (1.7 mmoles) of the epoxide **12** and 0.12 g. of sodium azide in 20 ml. of glacial acetic acid was stirred for 12 hours at room temperature. Then, the reaction mixture was poured over 100 ml. of ice-water and 1*N* sodium hydroxide was slowly added until *p*H 7 was obtained. The resulting suspension was stirred at room temperature for 10 minutes and filtered. The precipitate was washed several times with cold water. Thin layer preparative chromatography in benzene/ethyl acetate/chloroform (85/10/5) as eluent indicated the presence of two different compounds, but only the less retained major product could be isolated in enough yield for identification, affording 0.31 g. (55% yield) of the title compound, m.p. 184-186°; ir (nujol): ν max 3100-3500 (OH), 2110 (N_3), 1660 (C=O), 1620, 1460, 1380, 1315, 1260, 1215, 1060 (secondary OH), 760 cm^{-1}.

Anal. Calcd. for $C_{17}H_{15}N_5O_3$: C, 60.53; H, 4.45; N, 20.77. Found: C, 60.57; H, 4.42; N, 20.63.

3-Azido-4-methyl-4a,12a-diaza-3,4,4a,5,12,12a-hexahydronaphthacene-5,12-dione (**15**).

A solution of 0.25 g. (0.75 mmole) of the hydroxyazide **14** in 20 ml. of dimethyl sulphoxide was heated at 80° for 8 hours. After that, the reaction mixture was poured over 100 ml. of ice-water and filtered. The resulting precipitate was chromatographed under the same conditions described above in the synthesis of **14** to give 0.15 g. (64% yield) of **15**, m.p. 165-166°; ir (nujol): ν max 2105 (N_3), 1660 (C=O), 1625, 1460, 1420, 1340, 1280, 125, 920, 760, 725 cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}N_5O_2$: C, 63.95; H, 4.07; N, 21.94. Found: C, 63.78; H, 4.16; N, 21.67.

2-Hydroxy-2-methyl-3-bromo-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**6**) and 2-bromo-2-methyl-3-hydroxy-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**17**).

To a suspension of the epoxide **15** (0.6 g. or 2.0 mmoles) in 30 ml. of methanol, 10 ml. of 50% aqueous hydrobromic acid were added, and the mixture heated whilst stirring at 50° for 48 hours. After that, the suspension was filtered to give a creamy solid. The filtrate was treated with 20 ml. of chloroform, and the organic layer washed repeatedly with water and dried over magnesium sulphate. The solvent was removed by rotary evaporation and the dark-brown residue added to the precipitate obtained before. Thin layer preparative chromatography in benzene/ethanol (50/1) as eluent led to the isolation of 0.3 g. of a white solid which recrystallised from water and was shown to be a mixture of the isomers **17** (24% yield) and **6** (16% yield) in a 3/2 ratio on the basis of data obtained from the nmr spectrum (14).

1-Ethoxy-2-hydroxy-2,3-dimethyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**20**) and 1-hydroxy-2-ethoxy-2,3-dimethyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**21**).

To a cooled (0°) chloroform solution of **3** (0.5 g. or 1.8 mmoles in 50 ml.) 0.3 g. (1.8 mmoles) of *m*-chloroperbenzoic acid were added dropwise. The mixture was stirred for one hour at room temperature, and then refluxed for 5 hours. After that, stirring was maintained at room temperature for 12 hours more. The solution was treated with 10% aqueous sodium sulphite, for destroying the excess of peracid, and the organic layer successively washed with 5% aqueous sodium bicarbonate and water. After drying over magnesium sulphate, the solvent was removed by rotary evaporation. Purification of the residue by thin layer preparative chromatography in benzene/ethanol (94/6) as eluent led to the isolation of two different products, the more retained of which was identified as **20** (0.16 g., 27% yield); m.p. 191-194°; ir (nujol): ν max 3100-3600 (OH), 1645 (C=O), 1620, 1465, 1420, 1290, 1220, 1120 (tertiary OH), 770, 725 cm^{-1}.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.98; H, 5.94; N, 7.93. Found: C, 67.80; H, 5.86; N, 7.75.

The less retained product obtained in the thin layer chromatography described above was identified as **21** (0.26 g., 43% yield), m.p. 186-187°; ir (nujol): ν max 3200-3550 (OH), 3070, 1670 (C=O), 1645, (C=O), 1625, 1465, 1250, 1200, 1030 (secondary OH), 760 cm^{-1}; ms: m/e (% relative abundance) 354 (100, M^+), 309 (26), 279 (19), 278 (21), 265 (35), 239 (23), 238 (54), 226 (26), 225 (59), 212 (26), 210 (76), 198 (88), 180 (69), 127 (66).

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.98; H, 5.94; N, 7.93. Found: C, 67.67; H, 5.92; N, 7.97.

1-Hydroxy-2-ethoxy-2-methyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**23**) and 1-ethoxy-2-hydroxy-2-methyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**24**).

To a cooled (0°) chloroform solution of **4** (1.0 g. or 3.5 mmoles in 50 ml.), 0.6 g. (3.6 mmoles) of *m*-chloroperbenzoic acid were added dropwise. The mixture was stirred for one hour at room temperature, and then refluxed for 2 hours more. After cooling, the resulting solution was treated with 10% aqueous sodium sulphite, and the organic layer washed successively with 5% aqueous sodium bicarbonate and water, and dried over magnesium sulphate. The solvent was removed by rotary evaporation, and the remaining residue stirred for 15 minutes with 50 ml. of ethyl acetate. After that, the suspension was filtered and the filtrate evaporated "in vacuo" to give a residue (0.3 g.) which was identified as unreacted **4**. The precipitate recrystallised from water/acetone to give 0.4 g. (33% yield) of a yellow solid that melted between 113° and 116°, and was shown to be a mixture of isomers **23** and **24** in a 57/43 ratio; ir (potassium bromide): ν max 3100-3500 (OH), 1655 (C=O) 1645 (C=O), 1620, 1385, 1305, 1265, 1220, 1090 (tertiary OH), 1040 (secondary OH), 760 cm^{-1}.

Anal. Calcd. for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.88; N, 8.23. Found: C, 67.24; H, 5.81; N, 8.38.

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